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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,069	03/30/2001	Kenneth T. Wheeler	9151-6	8239

20792 7590 07/06/2005

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,069	WHEELER ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11,33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) *35* is/are withdrawn from consideration.

5)☒ Claim(s) *36, 37* is/are allowed.

6)☒ Claim(s) *1,4-7,11 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed 4/29/05 has been entered. Applicant has added new claims 35-37. Claims 36 and 37 directed to the elected invention of Group II will be examined. Newly submitted claim 35 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 35 directed to the non-elected group of XI, see restriction dated 10/02/03. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 35 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-7, 11 and 33 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 remains indefinite because it is not clear what activity $\sigma_{1\beta}$ exhibits that is termed a "σ2 activity" so as to allow the metes and bounds of the claim to be determined. Applicant argues the specification discloses $\sigma_{1\beta}$ exhibits a substantial increase in σ_2 –like binding and the ratio can be used as an indicator of the proliferate state of the cells. Applicant has not disclosed where in the

specification or prior art the σ2 activity of $\sigma_{1\beta}$ is defined. Does the activity refer to an activation of a compound, phosphorylation state, ligand binding, promotion of transcription etc? Without a clear definition of the activity the metes and bounds of the claim cannot be determined.

Claims 4-7 and 33 are indefinite because they depend on an indefinite base claim.

3. Applicant's arguments, filed 4/29/05, with respect to the rejection of claims 1, 5-7, 11 under 35 U.S.C. 101 and 33 have been fully considered and are found persuasive. The rejection of claims 1, 4-7, 11 under 35 of U.S.C. 101 has been withdrawn.

4. In view of withdrawal of the rejection under 35 of U.S.C. 101 the Examiner has recast the rejection under 35 U.S.C. 112, first paragraph to better address Applicant's rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5 Claims 1, 4-7, 11 and 33 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide comprising the nucleotide of SEQ ID NO: 1, encoding the polypeptide comprising the amino acid sequence of SEQ ID NO: 2, an expression vector comprising said

polynucleotide, an isolated cell comprising the expression vector, method for producing said polypeptide using said cell and an isolated transformed host cell comprising said polynucleotide, does not reasonably provide enablement for other polynucleotides or use of other polynucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to:

a) Isolated polynucleotide that has at least 95% homology to the polynucleotide of SEQ ID NO: 1 and that encode a σ1β receptor exhibiting σ2 activity.

b) Isolated polynucleotide that has at least 95% homology to the polynucleotide encoding the σ1β receptor SEQ ID NO: 2 and that encode a σ1β receptor exhibiting σ2 activity.

c) An expression vector comprising the polynucleotide of a) or b).

d) Cell comprising the expression vector of c).

e) Method for producing a protein comprising the amino acid sequence of SEQ ID NO: 2, or comprising a fragment thereof, said method comprising culturing a host cell comprising an expression vector comprising at least a fragment of the polynucleotide sequence of SEQ ID NO:1 encoding a σ1β receptor under conditions suitable for the expression of the protein

f) A transformed host cell comprising the polynucleotide of a) or b)

A review of *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the whether undue experimentation would be required to use the claimed invention.

Mach et. al. (see IDS, Cancer Research Vol. 57, 1546-161, 1997) disclose, although the expression of σ1 and σ2 receptors is heterogeneous, their function is unknown (see Abstract). Malliga et al (see IDS, The Journal of pharmacological and Experimental Therapeutics, Vol. 289, page 251-260) disclose the biochemical and pharmacological profiles of these receptors differ markedly, indicating species and cell type dependent differential expression of various subtypes of σ receptors in immune cells. (See page 252, column 1, first paragraph). Further WO 97/34792 (see IDS) also discloses the function of σ2 is unknown (see page 1). The σ1β receptor of instant invention is expressed in a wide variety of tissues, normal and cancerous. Therefore based on the art and the disclosure, the functionality of claimed σ1β receptor of SEQ ID NO: 2 is unknown. The definition of the activity of the σ1β receptor is not disclosed. Members of the σ1 receptor family are also highly divergent in their effects and ligand specificity. Based on the homology data of the σ1 receptor family and the

general classification into the superfamily of σ1 receptor family, the specification discloses the claimed σ1β receptor is useful for detecting, preventing and/or treating diseases associated with cancer. There is no clear nexus between the treatable diseases/disorders and use of claimed σ1β receptor. Even if a test compound in an assay for drug screening affects the expression of Applicant's individual σ1β receptor, the specification does not disclose any interpretation for the result, and none is known in the art. Applicants arguments that the ratio of σ1 to σ1β density is an indicator of proliferate state of the cells is found persuasive. Therefore the use of the polynucleotide of claimed invention lies in its ability to be used to determine the proliferative status of cells that express said receptors. The methods are carried out by contacting the cells with a detectably labeled σ1 receptor ligand (Net [^{3}H]Pent and a detectably labeled σ1β receptor ligand (Net[^{3}H]DTG), and determining the extent to which the ligands bind to the cells, wherein the extent provides a measure of the proliferative status of the cell. The respective densities of σ1 receptors to the density of σ1β receptors of the cell, are indicative of the proliferative status of the cell, wherein a higher density of σ1β receptors as compared to σ1 indicates that the cells are in a proliferative state. The receptor of SEQ ID NO:2 has been shown to bind Net[^{3}H]DTG. A specific binding is critical to determining the correct ratio of the two receptors that will allow for it use. If the claimed receptor is mutated and it affects the binding of Net[^{3}H]DTG to said receptor then the method, which provides the invention its use, will no longer be valid. The claimed activity σ1β receptors that must be retained by the variants encompassed by the claims is not disclosed. The

variants that will produce the undefined activity and still retain the ligand binding properties of the receptor of SEQ ID NO:2 are not disclosed. Any mutants that have an undefined activity as claimed but do not retain ligand-binding properties and effect the determination of the respective densities of respective densities of σ1 receptors to the density of σ1β receptors of the cell receptors of the cell will be no longer useful. Applicant has not disclosed how to use said receptor variants. Further such variants may be differentially expressed in which case even the determination of ratios of densities of σ1 receptors to the density of σ1β receptors may not provide an accurate indication of cell proliferation, if at all. The variant may not even bind Net[^{3}H]DTG, therefore be useless in the assay. Applicant has not disclosed which residues on the polypeptide are involved in ligand binding. The critical feature of the invention that relates structure to function is not disclosed. The percent homology limitation of the claims encompasses billion of possible structures and no clear defined activity. It would take undue experimentation to make and use the polynucleotides encompassed by the claim. To overcome the rejection Applicant must show how specific variants with a defined assayable activity can be made without undue experimentation, said variants retaining the ability to bind Net[^{3}H]DTG in such a manner that when compared to Net [^{3}H]Pent σ1 receptor binding they are indicative of the proliferative status of the cell, wherein a higher density of σ1β receptors as compared to σ1 indicates that the cells are in a proliferative state.

(1) The quantity of experimentation necessary

Even though the skill of the artisan in the art of molecular biology is high, undue experimentation is required to make functional σ1β receptor variants. The specification has not disclosed the use of non-functional variants. The claims encompass billions of variants (see the rejection under Written Description for the algorithm that can be uses to determine the variants) with no specific activity. Further, the $\sigma_{1\beta}$ receptor activity that is termed a "σ2 activity" is not disclosed

(2) The amount of direction or guidance presented

The production of polynucleotides that encode functional σ1β receptors variants, encompassed by the claims, requires knowledge of a common property or critical technical feature of the genus claimed. The production of functional variants requires that conserved regions, which are critical to the structure, and function of the protein be known. There is no disclosure of said conserved regions, which are critical to the structure, and function of the protein. There is no description of the sites at which variability may be tolerated. There is no information regarding the relationship of structure to function. There is no clear evidence of the activity possessed by the claimed genus of nucleic acid molecules encoding variant σ1β receptor polypeptides. Substitutions/addition/deletions that result in active variants are not disclosed. Substitutions/addition/deletions that are detrimental to σ1β receptor variant activity are not disclosed. A person skilled in the art would not know how to make and use the claimed invention so that it would operate as intended without undue experimentation.

(3) The presence or absence of working examples

The disclosure fails to provide a representative number of species and structural data to enable the production and use of the genus as broadly claimed.

(4) The nature of the invention

Isolated polynucleotide encoding σ1β receptor variants is claimed. The claims encompass billions of variants with no specific defined activity. Also what will be use of producing a fragment that is completely unrelated to the polypeptide of SEQ ID NO:2, since such fragments are encompassed by claim 11. A fragment can encompass only the 5% of the polypeptide sequence that is not included in the 95% homology.

(5) The state of the prior art

The genus of σ1 has diverse functions and compound specificity (disclosed above). Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants σ1β receptor would have the same functionality as the protein disclosed in SEQ ID NO:2, since no activity is disclosed It can also not be predicted which variants contain the domain(s) of SEQ ID NO:2, containing the critical special technical feature of the claimed σ1β receptor, since no critical special technical feature is disclosed in the specification or prior art. Prior art does not disclose the production of functional σ1β receptor variants.

(6) the relative skill of those in the art

Although skill in the art is high, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides that would enable the production of functional variants encoding σ1β receptors.

(7) The predictability or unpredictability of the art

Prior art discloses the complexity of producing functional variants. It is also difficult to predict function from structure. Bowie et al (Science, March 16, 1990, Vol. 247, pages 1307-1310, see prior Office Action) discloses that the function of a protein cannot be predicted from the sequence of a protein (page 1310, column). Mutating proteins by amino acid substitutions can have a dramatic effect on function. The location of the mutation and the type of amino acid substituted is critical for protein functionality (page 1037, column 2). For example, replacing the Asp in the catalytic triad of trypsin with Asn results in a 10^4-fold reduction in activity (page 1307, column 2). Based on the disclosure of Bowie it can be concluded that mutations in residues that are required for structure formation or stability can have dramatic effects on activity.

(8) The breadth of the claims

The claims encompass nucleic acid comprising variants of SEQ ID NO:1 and encoding variants of the polypeptide of SEQ ID NO:2. The variants may be completely unrelated, structurally and functionally to the protein encoded by the nucleic acid of SEQ ID NO:1. The claims are drawn to an orphan σ1β receptor. Neither the claims nor the specification disclose what specific biological activity is associated with the claimed σ1β receptor or what specifically classifies a protein as a σ1β receptor. Therefore, nucleic acid encoding unrelated and inactive

proteins are encompassed by the claims. The specification does not disclose how to produce active variants with ligand binding properties to be useful or how to use inactive ones encoded by polynucleotides that have, for example, at least 95% homology to the polynucleotide of SEQ ID NO:1, comprise fragments of the polynucleotide of SEQ ID NO:1, or encode fragments of the polypeptide of SEQ ID NO:2.

Therefore, many of the polynucleotides that have at least 95% homology to the polynucleotide of SEQ ID NO:1 may be unrelated to the nucleic acid encoding the polypeptide of SEQ ID NO:2. Also, many of the polynucleotides that have at least 95% homology to the polynucleotide encoding the polypeptide of SEQ ID NO:2 may be unrelated to the nucleic acid of SEQ ID NO:1. The specification does not disclose how to produce active variants. The specification does not disclose how to use inactive polypeptides encoded by claimed nucleic acid molecule. Also, the specification does not disclose how to use unrelated polypeptides (i.e. functionally unrelated to σ1β receptor) encoded by claimed nucleic acid molecule. The claimed nucleic acid encodes a σ1β receptor whose functionality has not been disclosed. Neither the claims nor the specification disclose what specific biological activity is associated with the claimed σ1β receptor.

Therefore, undue experimentation is necessary to make and identify the polypeptides with the structural and functional features of instant invention. There is a the lack of direction/guidance presented in the specification regarding the synthesis, identification, purification, isolation and characterization of the

variants polypeptides encoded by the claimed polynucleotides. Due to the unpredictability of the effects of mutation on the structure and function of proteins, and the breadth of the claims which fail to recite critical feature of the invention as it relates structure to function, undue experimentation would be required of the skilled artisan to make or use the claimed invention as claimed. Therefore, it would require undue experimentation to practice this invention as claimed, because the skilled artisan would have no reasonable expectation that claimed σ1β receptor variants could be made and used for any specific purpose. Further the nucleic acids that comprise variants of SEQ ID NO:1 or encode variants of the polypeptide of SEQ ID NO:2 may not specifically hybridize to the polynucleotide of SEQ ID NO:1 or to the polynucleotide that encodes the polypeptide of SEQ ID NO:2. Applicant has not disclosed how to use said nucleic acids that do not specifically hybridize to the polynucleotide of SEQ ID NO:1. Further the specification does not disclose how to use nucleic acids that comprise variants of SEQ ID NO:1 or encode fragments or variants of the polypeptide of SEQ ID NO:2 without functional activity.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to make and use the invention. As is evidence in the discussions *supra*, each of *Wands* factors has been carefully considered in the instant grounds of rejection, and it is maintained that undue experimentation would be required by the skilled artisan to make and use the instant invention.

Further, the vector comprising the claimed nucleic acid, the cell comprising said vector, the cell comprising said nucleic acid, and the method of producing

polypeptide encoded by claimed nucleic are also rejected under 35 U.S.C. 112, first paragraph, for the reason given above.

Claim Rejection 35 *USC* § 112, 1st paragraph (Written Description)

6. Claims 1, 5-7 and claims 33 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues that the structure of the invention has clearly been established and one of skill in the art could readily predict the structure as claimed. Applicant also argues that the codon usage of the claimed variants can be selected depending on the desired properties and in accordance with the host organism or cell. Also argued is that the person of skill in the art can readily envision active variants of SEQ ID NO:1 and 2. Applicant's arguments have been fully considered but are not found persuasive. The amendment of claim 1 to include 95% homology and addition of "$\sigma_{1\beta}$ exhibiting σ_2 activity" does not overcome the rejection of record. What is the σ_2 activity" exhibited by $\sigma_{1\beta}$.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a

mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNAs that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Also, where a claim purports to cover all nucleic acids that encode a specific protein and the specification discloses but a single DNA known to do so, the situation is analogous to a single means claim and does not meet the enablement requirement under para. 1 of ∋112. The court has also held that a claimed nucleic acid could meet the written description and enablement requirements if the nucleic acid were defined by a disclosed process found, after-the-fact, to produce the nucleic acid, and claimed as a product-by-process. However, in the instant case, the nucleic acids are not claimed as a

product-by-process, nor does the specification disclose any process known to yield a claimed nucleic acid.

The only difference between the cases reviewed by the court and Board, and the instant case, is that in addition to recitation of the desired protein activity, the claims also recite a broad arbitrary structural relationship between the claimed nucleic acid sequence, either in terms of its nucleotide sequence or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. Consequently, the claims do not purport to claim *all* nucleotide sequences, which encode a particular functional protein. However, this distinction does not aid Applicant's cause. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision in numerable species of nucleic acid sequences that are at least a given % identity to a reference nucleotide sequence and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide classified as σ1β receptor. The fact remains that the actual nucleic acid sequences which encode a protein classified as σ1β receptor

or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a σ1β receptor with 95% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a σ1β receptor than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}) . The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given

% identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}. For a 300-nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56}.

In the present case, the reference amino acid sequence, SEQ ID NO:2 is 192 amino acids long, and the reference nucleotide sequence, SEQ ID NO:1 is 597 nucleotides long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least 95% identical to the reference amino acid sequence or nucleotide sequence, would be billions. While limiting the scope of potential sequences to those that are at least 95% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the

claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those, which encode a σ1β receptor. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for σ1β receptor activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a σ1β receptor polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of a as σ1β receptor known that have structural homology with SEQ ID NO:2, with same ligand specificity and activity, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be

determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only one putative functional amino acid sequences, SEQ ID NO:2, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining polypeptide variants of SEQ ID NO:1, which would be suitable.

The claims also encompasses nucleic acid comprising fragments (variants) of SEQ ID NO:1 or fragments (variants) encoding the polypeptide of SEQ ID NO:2 encoding variants of the protein disclosed in SEQ ID NO:2, said variants may be completely unrelated, structurally and functionally to the protein encoded by SEQ ID NO:1 .

The common function of the nucleic acid (SEQ ID NO:1) encoding the polypeptide (SEQ ID NO:2), which is based upon a common property or critical technical feature of the genus claimed is not disclosed. The claims, as written, encompass nucleic acids encoding polypeptides, which vary substantially in length and also in amino acid composition. The instant disclosure of a polynucleotide of SEQ ID NO:1 encoding the polypeptide of SEQ ID NO:2 does not adequately describe the scope of the use of the claimed genus, which encompasses a substantial variety of subgenera including polynucleotides encoding full-length proteins, comprising fragments of SEQ ID NO:1 or variants

encoding polypeptides classified as σ1β receptor, chimeric constructs, fusion constructs, which may encode polypeptides completely, unrelated functionally to the polypeptide of SEQ ID NO:2. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Instant specification fails to provide sufficient descriptive information, such as definitive structural and functional features of the claimed genus of polypeptides. There is no description of the conserved regions, which are critical to the structure, and function of the genus claimed. For example, what regions and fragments of the claimed σ1β receptor contain a definitive structural feature required for protein function? The specification proposes to discover other members of the genus by using screening assays and techniques involving probes, primers, and hybridization. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed. No identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to

predictably identify the encompassed molecules as being identical to those instantly claimed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide and nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe, enable and use the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. It is acknowledged that the skill of the artisan in the molecular biology art is high. However, in the current instance, **there is no clear evidence of activity possessed by the claimed genus of nucleic acid molecules encoding variant σ1β receptor polypeptides, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the genus claimed relates to function.** Because of the lack of guidance in the prior art and current application, one skilled in the art could not predict if the variants σ1β receptor have the same activity as the protein disclosed in SEQ ID NO:2, since no activity is disclosed, or if they contain the domain(s) of SEQ ID NO:2, containing the critical special technical feature of the claimed σ1β receptor, since no critical special technical feature is disclosed.

The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid or polypeptide is itself is required. See *Fibers v. Revel*, 25 USPQ d. 1601 at 1606 (CAFC 1993) and *Amen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an

adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Therefore the specification fails to disclose the activity of the claimed genus of σ1β receptor, the critical special technical feature of the polypeptides or how the critical special technical feature encompassed by the fragments and variants of claimed σ1β receptor relates to function.

The claims encompass nucleic acids encoding proteins, which are structurally and functionally unrelated to the protein/nucleic acid disclosed in SEQ ID NO:2 and 1, respectively. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of nucleic acids . There is no description of the conserved regions, which are critical to the structure, and function of the genus claimed. The claimed nucleic acid encodes an orphan σ1β receptor whose activity has not been disclosed. The complexity of assigning a function and membership into a the genus of σ1 receptors is highlighted by the diverse function/compound specificity of σ1β receptors disclosed above (IDS). Neither the claims nor the specification disclose what specific biological activity is associated with the

claimed σ1β receptor or the special technical feature encompassed by specific domains associated with a specific activity of the claimed genus. The superfamily of σ1 receptor are specialized proteins designed for chemical recognition of ligands, and subsequent transduction of information encoded in those ligands/compounds to the machinery of the cell. The σ1 receptor interacts with many diverse compounds having diverse effects. The important features, which would help to define the σ1β receptor activity and define the genus claimed, have not been disclosed in the specification nor prior art. Further the activity transduced is not disclosed or how it relates structure to function.

The claims encompass nucleic acids encoding proteins, which are structurally and functionally unrelated to the protein of SEQ ID NO:2. Therefore instant specification fails to provide sufficient descriptive information, such as definitive structural/ functional features of the claimed genus of polypeptides. There is no description of the conserved regions, which are critical to the structure, and function of the genus claimed. Further, the vector comprising the claimed nucleic acid, the cell comprising said vector, the cell comprising said nucleic acid, and the method of producing polypeptide encoded by claimed nucleic are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 33 remains rejected under 35 U.S.C. 102(b) as being anticipated by Malliga et al (See IDS, The Journal of Pharmacological and Experimental Therapeutics, Vol. 289, page 251-260).

Applicants argue the claim is only anticipated if each and every element as set forth in the claim is found, either expressly or inherently described, in a single art reference. Applicants argue the Malliga reference fails to anticipate the claim. Applicants' arguments have been fully considered but are not found persuasive.

Malliga discloses transformed Jurkat T lymphocyte cells containing the polynucleotide of claim. Although the cells are not transformed with the polynucleotide of claim 1, the cells disclosed are transformed with some other polynucleotide. Jurkat T lymphocyte cells meet the limitations of claim 33 because they inherently contain the cDNA polynucleotide of claim 1, absent evidence to the contrary. Therefore Malliga discloses a transformed host cell. The host cell of Malliga inherently comprises the polynucleotide of claim 1.

8. Claims 36 and 37 are allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa can be reached on 571272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi NSB
Art Unit 1646
July 1, 2005

JOSEPH MURPHY
PATENT EXAMINER